EUnetHTA JA3 WP4 - Other technologies, OTCA27
Comparative effectiveness of surgical techniques and devices for the treatment of benign prostatic hyperplasia (BPH)
External expert comments and manufacturer factual accuracy check

External expert comments

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
Franco Bergamaschi	10	262	Treatment is indicated in patients with BOO	2	Thanks, we now specify it better
Iain Robertson	10	271-272	Non- inferiority of minimally invasive options should not be the benchmark- the approach needs to be more patient centered. There is a trade off for minimally invasive technologies of a less invasive risks/ disruption to life for a somewhat inferior outcome either in duration or effect and for some patients this will be their decision. Therefore we do need to determine the effectiveness of the treatment but should not assume that inferiority would discount it.	1	Agree. The paragraph has been modified highlighting patients' trade off between effectiveness and quality of life
Iain Robertson	11	308	Remove "among them"	3	Done thanks
Iain Robertson	12	333/4	Duplicated line	3	thanks
Iain Robertson	12	334	"some of the available RCTS and pooled data" is not clear, do the authors mean- Pooled data that was based RCTs containing data suitable for extraction	2	Rephrased: Pooled data and, when pooling was not possible, some of the available RCTs showed
Iain Robertson	12	337	" for the latter outcome" would be more readable by simply stating the outcome	3	Replaced thanks
Iain Robertson	12	347-349	This sentence needs to be revised as it is very difficult to track which outcome is being referred to- particularly for PAE and PUL	3	Rephrased, thanks
Iain Robertson	13	383	Remove viceversa	3	Done thanks

EUnetHTA JA3 WP4 - Other technologies, OTCA27
Comparative effectiveness of surgical techniques and devices for the treatment of benign prostatic hyperplasia (BPH)
External expert comments and manufacturer factual accuracy check

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
Iain Robertson	14	400	Should state in particular for TURP	3	Done thanks
Iain Robertson	14	411	This sentence should be split to improve readability. Suggest second sentence beginning "Several of the technologies showed evidence of effect, improving or worsening, on urinary tract infections and incontinence.		Rephrased as suggested, thanks
Franco Bergamaschi	15	438	Bph rarely progress to carcinoma ? Must to be verified , suggestion : avoid	2	Corrected, thanks
Franco Bergamaschi	19	610-622	I'm not sure about laser called and described as " technical similar toTURP" TmLrp seems similar tuip (incision) and Holrp is similar to a partial enucleation: need to be checked .	1	This technique is described in several sources and we changed the reference to another one which lists these techniques as different techniques (Montorsi F, Saitta G, Suardi N. Chapter 13 - Surgical Treatment for LUTS/BPH: Laser Devices. In: Morgia G, Russo GI, editors. Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia: Academic Press; 2018. p. 257-88.)
Iain Robertson	24	827	The use of the word experimental is not appropriate as this would imply that in all the countries served by the guidelines this should only be available within a clinical trial. This is not the recommendation from both the guidelines which are discordant The American Urological guidance cites the evidence but offers expert opinion on factors not assessed by the evidence (technical ability/ low volumes centres etc) as the basis for their judgement. The European guidelines are more appropriate and I agree with their	1	Removed the word "experimental"

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
			evidence and analysis – with the available evidence – PAE delivers inferior outcomes for objective measurements I would remove "experimental" as this technique is in use throughout Europe, indeed NICE have evaluated the technique for general use in the UK.		
Iain Robertson	35	1091	Remove" eventually"	3	Done thanks
Iain Robertson	36	1105	I do not understand the meaning of the sentence starting "As for Indirectness"	3	Rephrased thanks
Iain Robertson	66 and subsequent	Table/ Graph	Would it be possible to include the comparator and the outcome in the tile of the illustrations eg. table on page 66 title "IPSS at 1 month" but the heading for this section is on page 64. Would be easier to read as HoLEP vs TURP: IPSS at 1 month. Also applies to all subsequent tables.	3	It would be a bit cumbersome at this point, sorry (working always on tight schedules, concentrating on key aspects which are still many in this cumbersome report)
Iain Robertson	215 and subsequent	396	"for the latter outcome" suggest would be clearer by simply stating the outcome eh statistically significant improvements in….	3	Done thanks
Iain Robertson	216	417	This comes across as inferring doubt in the authors mind and that a technique should only be used if it results in better functional outcomes. In practice, patients may choose a technique that is less invasive accepting that it has an inferior functional outcome.	2	Thanks. We rephrased: "This could imply that proposed techniques are intended to offer patients less invasive alternatives while accepting not to improve functional outcomes. If this is the case, it should be noted that authors and sponsors do not try to have statistical power to demonstrate

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
					improvements in outcomes which may benefit from lower invasiveness."
Iain Robertson	218	505-507	As previous comments, some of these techniques may produce inferior outcomes but may still be used as they are less invasive- this is fairly common in practice -	1	Rephrased: Minimally invasive technologies are expected to reduce short and long-term side effects of standard surgical treatments for BPH (in particular of TURP) even if this should result in lower effectiveness on functional outcomes"
Iain Robertson	General	General	?Why was the RCT by Gao not included (not in either include or excluded trials) Gao et al Radiology 2014 Mar;270(3):920-8.doi: 10.1148/radiol.13122803.	2	Both this RCT and the one in your next comment were missing from our initial search, in spite of having included key words for PAE in our search strategy. We are now including these two RCTs: thanks for pointing them out!
Iain Robertson	General	General	Why was the RCT by Carnevale not included(not in either included ir excluded trials) Carnevale Cardiovasc Intervent Radiol 2016 Jan;39(1):44-52. doi: 10.1007/s00270-015-1202-4. Epub 2015 Oct 27	2	See previous comment
Iain Robertson	General	General	For all the less established techniques I do think the restriction to RCT potentially disregards a significant volume of literature that would provide useful information. I appreciate the metric of RCT for effectiveness but particularly for safety information there is often a considerable volume of evidence for safety within non RCT and registries that is simply being ignored by this approach	2	You are right. Unfortunately this report includes 21 technologies and almost 100 RCTs. Extending the search and analyses to observational studies would have been simply unfeasible. This Is also an important warning (for us and for HTA authors in general) not

EUnetHTA JA3 WP4 - Other technologies, OTCA27
Comparative effectiveness of surgical techniques and devices for the treatment of benign prostatic hyperplasia (BPH)
External expert comments and manufacturer factual accuracy check

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
					to embark in extremely complicated and plethoric assessments that may lead to a reduced depth of analysis

Manufacturer fact check comments

Comment from *Insert your company's name*	**Page number**	**Line or section number**	**Description of factual inaccuracy and proposed amendment** *Please insert each new comment in a new row.*	**Character of comment** • **'major'[a] =1** • **'minor'[b] = 2** • **'linguistic'[c] =3** *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Authors' reply**
Teleflex Medical	11	298-300	Prostatic Urethral Lift (PUL), using small *adjustable* permanent implant [...] the urethra; *creating an open channel to increase the urine flow* Suggestion: follow same structure for all devices. Description of the device, what it does (technique) and what it obtains.	1 & 3	Thank you. We added adjustable and the suggested text. We also aligned the structure for all devices.

Teleflex Medical	13	368-369	On the section ***Safety: direct comparisons:*** There is global statement: *The available comparison did not show differences for bladder perforation […] neck contracture* The characteristics of some techniques avoid some of the complications mentioned in that statement. Suggestion: review if that statement can be modified based on different techniques, and not applicable as global.	2	Thanks for the suggestion. In principle we agree but, having 21 technologies and plenty of outcomes to assess, we consider it difficult to make specific comments on outcomes pertaining or not pertaining to specific technologies (especially in an executive summary)
	13	370 – 385	All these statements need to be referenced. It is important to know which studies are being cited in order to be able to assess the factual accuracy.	1	This is an executive summary, summarizing the findings from analyses we performed and presented more in depth in the subsequent chapters of the report
Teleflex Medical	13	379	In the case of Urinary tract Infection, it is only compared vs HoLEP and PAE as favourable. Suggestion: Consider to add PUL as favourable, by taking into account the result from the LIFT study: 2.9% at 3 months and 0% at 1 year (from 3-12months). (LIFT RCT: *C. Roehrborn C et al. Journal of Urology 2013; C. Roehrborn C et al. The Canadian Journal of Urology 2017*)	1	Our inclusion criteria did not consider sham controlled study, unless active controlled trials were not available
Teleflex Medical	13	382	Catherization is a procedure not a complication, If catheterisation is happening post-procedure it is being done in response to a complication such as retention but the action of catheterisation itself is not a complication.	1	Re-catheterization was one of the outcomes the assessment team agreed with experts and dedicated reviewers. We assessed it as one of our outcomes of interest
Teleflex Medical	14	411-414	In paragraph 407-410 procedures which show an advantage vs TURP on the impact on sexual function are specified. Suggestion: be specific in lines 411 to 414 regarding which technologies are being referred to.	2	This is a “concluding summary” paragraph synthesizing information provided in previous paragraphs of the executive summary. The latter is anyway a summary synthesizing information provided in the core parts of the report

Teleflex Medical	18	555-556	**Not only all lasers use normal saline instead of distilled water to avoid TUR syndrome.** Suggestion: check all minimally invasive technology procedure		This paragraph is about lasers only. It is mentioned in other techniques as well e.g. B-TUVP.
Teleflex Medical	18-24		If feasible mention same features description) (and structure for all technologies; as for example: - Type of anaesthesia - Inpatient/ day case/ ambulatory procedure - Rate and length of catheterization - Timing of the procedure - Pvr, qmax, ipss—this is mentioned for UroLift in the technique description but not for the others. - Prostate volume (from guidelines or studies) - Complications - Patient experiences: as for example pain; recovery time, etc. As it is written by now, it is not homogenous, and it is hard to make a comparison among alternatives. Specify references for each technology's description	1	Unfortunately, it was not possible as the description of many of these techniques was very short in the literature and it was not feasible to find all this information for all the techniques, so a complete uniformity was not possible. We specified references to all of the technologies, we are not sure where you are missing a reference. We deleted the PVR, Qmax and IPSS specifications from the PUL procedure as this was not mentioned in your IFU.
Teleflex Medical	24	818	"The PUL implants consist of an elastic nitinol" Comment: Nitonol is not elastic, this is factually incorrect	1	Thank you we corrected.

	24	815-826	**"Prostatic urethral lift** (PUL): small permanent implants which take the form of sutures are placed by a hand-held device through a cystoscope transurethrally. The implants mechanically open the urethra and relieve obstruction. PUL is performed using the Urolift device, which was developed in 2004 [20, 23]. The PUL implants consist of an elastic nitinol capsular tab, a polyethylene terephthalate monofilament, and a stainless-steel urethral end piece [54]. PUL can be performed under local anaesthesia with oral or intravenous sedation. It can also be performed in men with blood clotting disorders or men receiving anticoagulant therapy, hence it is suitable for men at high risk of general anaesthesia. Prostate volume between 20 mL and 70 mL, IPSS of 12 or greater, a measured Qmax of 15 mL/second or less, and PVR of less than 350 mL are typical patient selection criteria. PUL is unable to treat a median lobe of the prostate which causes obstructive intravesical protrusion of the prostate [55]." Comment: Please correct to the following to reflect the indications of the device: **Prostatic urethral lift** (PUL): small permanent implants which take the form of sutures are placed by a hand-held device through a cystoscope transurethrally. The implants mechanically open the urethra and relieve obstruction. PUL is performed using the Urolift device, which was developed in 2004 [20, 23]. The PUL implants consist of an ~~elastic~~ nitinol capsular tab, a polyethylene terephthalate monofilament, and a stainless-steel urethral end piece [54]. PUL can be performed under local anaesthesia with oral or intravenous sedation. ~~It can also be performed in men with blood clotting disorders or men receiving anticoagulant therapy, hence it is suitable for men at high risk of general anaesthesia~~. Patients with prostate volumes between 20 mL and 70 mL, IPSS of 12 or greater, a measured Qmax of 15 mL/second or less, and PVR of less than 350 mL have been commonly studied, however the procedure is indicated to treat prostate volumes up to 100cc without restrictions on baseline characteristics such as IPSS, Qmax, and PVR.. ~~are typical patient selection criteria~~. PUL is also ~~unable~~ indicated for the treatment ~~to treat a~~ of median lobe obstruction ~~of the prostate which~~ a form of obstruction that causes ~~obstructive~~ intravesical protrusion of the prostate [55].	1	Thank you for pointing out. We used the NICE MTG26 as a source where it was described as a superelastic nitinol capsular tab. We removed the word elastic. We also removed the line regarding clotting disorders and anticoagulant therapy. We also changed the part on the middle lobe (see reply below).

Teleflex Medical	24	824-826	"PUL is unable to treat a median lobe of the prostate which causes obstructive intravesical protrusion of the prostate " Comment: The sentence above (especially the word *unable*) is not correct. An existing study (MEdLift Study) was designed to and successfully showed that prostates with median lobe obstruction, can be treated with the PUL procedure safely and effectively. (Daniel Rukstalis, Douglas Grier, Sean Stroup, Ronald Tutrone, et al., 2018, *"Prostatic Urethral Lift (PUL) for obstructive median lobes: 12 month results of the MedLift Study")* "Unable" is not used in any other guidance and both the FDA and NICE (forthcoming May 4th) have changed their guidance to remove the restriction on treatment of median lobes	1-3	Thank you for the correction. The source we referenced used the term unable and the NICE 2015 guidance also stated "However, the company's training materials recommend that the system should not be used in men whose prostate has an obstructing middle lobe." We changed the paragraph to reflect the current research findings. As the new NICE guidance is not published yet, we cannot reference that, so we will refer to the Instructions for Use material on your website.
Teleflex Medical	27	897. Table 2.1. Population	Rationale: According to the *guidelines [...]* Please, specify this refers to the American Guidelines (AUA); and not the European guidelines (EAU)	3	Added, thanks

Teleflex Medical	28	897. Table 2.1. Outcomes	**Quality of life measures (generic)** Please, specify it refers to IPSS QoL **Persistent irritative symptoms:** There is a description of this complication in page 33, line 983-988; which defines this complication and specifies that is it included *early irritative symptoms* If those early irruptive symptoms would have been separated and classified in the group of complications: , **postoperative complication**, which we think it is more accurate; then outcomes would change within the different alternatives. **Recatheterization** Catherization is a procedure not a complication, If catheterisation is happening post-procedure it is being done in response to a complication such as retention but the action of catheterisation itself is not a complication.	1	RCTs often do not specify which quality of life measure has been used (even if IPSS QoL is the likely outcome assessed most of the times). By specifying “IPSS QoL” we would have not considered relevant QoL data. As for irritative symptoms, we think that they are related to BPH more than a complication of the surgery. As for re-catheterization, as you say it is done in response to a complication, therefore in our opinion it can be listed among the postoperative complications. We could say that also blood transfusion is a procedure, which is done in response to blood loss.
	30		“Migration rate of stent (PUL)” Please correct to the following as PUL is not a stent: Migration rate of the implant (PUL)	1	Corrected, thanks

Teleflex Medical	38-40	4.2. Studies included in the assessment	If WAVE therapy is included Vs Sham why are other RCT trials Vs sham excluded? PUL Vs Sham should be included or WAVE Vs Sham excluded. The comparative analysis would be strengthened by the inclusion of the L.I.F.T. study, i.e., the RCT (PUL vs sham) IDE pivotal study with 5yr patient follow-up, which led to FDA clearance. It has been well documented in population studies of BPH that there is a high percentage of men that discontinue medication and yet do not undergo traditional surgery. Recently Young et al. 2018 (Ann R Coll Surg Eng) reported that the prevalance of TURP has significantly declined over the past three decades, indicating patients seek other options. Minimaly invasive surgical therapy (like PUL) seeks to address unmet needs posed by traditional surgery such as preservation of sexual function, low risk of post-operative catheterization and hospital stay, and low risk of post-operative complications such as stricture and fulgeration. Under parameters reviewed and approved by the FDA, the comparator to sham (and not TURP) was sufficient to establish the value PUL provides patients.	1	Our inclusion criteria did not consider sham controlled study, unless active controlled trials were not available (as it is the case for WAVE)
Teleflex Medical	42	Table 4-3 row 2 column 6	“Mean prostate volume “ Comment: Please specify the unit of measurement (cm3)	2	Thanks, we added ml
Teleflex Medical	145	4.4.1.10.3	- Apply same structure of evaluation as previous technologies - Check patient selection (prostate volume); volume range. -Safety comparison analysis missing	1	Prostate volume and range is specified (sere pag 146). Safety outcomes are assessed in the section of the repost pertaining to safety (see pag. 190)

	146		Description of BPH6 could also include: The BPH6 responder endpoint assesses symptom relief, quality of recovery, erectile function preservation, ejaculatory function preservation, continence preservation, and safety. Preservation of ejaculation and quality of recovery were superior with PUL ($p < 0.01$). Significant symptom relief was achieved in both treatment arms. The study demonstrated not only noninferiority but also superiority of PUL over TURP on the BPH6 endpoint.	2	BPH6 is a composite endpoint. Our (predefined) list of outcomes includes some of its components, the ones we made comments on. As for safety outcomes, please see pag. 190
Teleflex Medical	190	58-60	*There were no data on bladder perforation, bladder and ureteral injury, capsular perforation, intraoperative mortality, reduction of serum sodium, catheterization time, TUR syndrome, bladder neck contracture, catheterisation, postoperative LUTS and long-term mortality.* T**his statement is suggested to be evaluated,** if applicable, **for all technologies** as it has been only specified or included in some technologies with no rationales; whereas in others this statement is missing. Due to the rationale of this assessment, we suggest **to verify** if there is no data on catheterisation time and recatherisation (retention) for UroLift. Specified in: BPH 6 RCT- *Sonken J, et al. 2015 European Association of Urology. Which for UroLift the rate of catheterization Is lower than for TURP* *And in LIFT RCT: Roehrborn C et al. Journal of Urology 2013. The length of catheterization is 0.9 day* Furthermore, the statement “there were no data on bladder perforation, bladder and ureteral injury, capsular perforation…” incorrectly reads as if there was no attempt to collect these data, when in reality these events did not occur.	1	For each technology we have listed the outcomes assessed in each of the studies assessing that technology. Where not specified, the outcomes which were not assessed can be easily deduced (missing from those listed in the PICO). Our idea was to facilitate readers by actively listing them, but some limited heterogeneity in reporting may be present across this ponderous report. If time allows, we’ll try to fix it. Anyway, we’ll eliminate the phrase you point at so that no controversies arise whether data were not collected or simply did not occur. As for catheterization time and re-catheterization, no data were available for the specific outcomes of interest in the two papers we had selected (according to our inclusion criteria).

Teleflex Medical	191	60 (Table)	Acute urinary retention and Urinary Tract Infection, please refer where this data comes from for UroLift and TURP. Suggestion: check data from the RCT LIFT Study (*Roehrborn C et al. Journal of Urology 2013); with a result on acute urinary retention: 0.7% at 3 months and 1 year for PUL; and for Urinary Tract Infection: 2.9% at 3 months and 0% at 1 year for PUL.*		As previously mentioned, the LIFT study was not consistent with our inclusion criteria and had been excluded.
	192		"On the other side, PVP, DioLVP, TUMT and PUL show statistically significant worsening of this outcome comparing to TURP, although only for PUL this result could be clinically relevant (confidence interval crossing the MCID)." Comment: Please clarify 'on the other side' as the comparison is unclear Please also revise the following sentence: On the other side, PVP, DioLVP, TUMT and PUL show statistically significant ~~worsening~~ differences ~~of~~ in this outcome ~~comparing~~ compared to TURP, although only for PUL this result could be clinically relevant (confidence interval crossing the MCID)."	2	With "on the other side" we intended that the direction of effect is opposite comparing to what is described in the preceding point (this time is in favour of TURP). Anyway, "on the other side" is not necessary and we took it out. The rest of the sentence should not be changed, otherwise readers cannot understand if the listed technologies are better or worse than the comparator.
	196		Please see prior comments as it also applied here in regards to Qmax		See previous comment.
	198		Please see prior comments as it also applied here in regards to Qmax		See previous comment.

	214		prostatic urethral lift (PUL), using small permanent implants: one end is anchored in the urethra and the other is attached to the firm outer surface of the prostatic capsule, so pulling the prostatic lobe away from the urethra For complete accuracy please revise description of the PUL procedure to read: The Prostatic Urethral Lift procedure involves the cystoscopically guided transurethral deployment of small permanent UroLift implants transversely across the lobes of the prostate. The implant is deployed such that the nitinol tab is anchored on the capsular surface and a tensioned suture is affixed to the urethral surface by a stainless steel urethral endpiece. Because the glandular stromal tissue of the prostate is compliant and more easily compressed outwardly, compression results in the opening of the prostatic urethra	1	We revised this in the Executive summary as well and used the same text in both the Discussion and the Executive Summary. The detailed description you provided is already covered in the TEC chapter in the detailed description of the technology.
	214		According to the American Urologic Association, some techniques (like HoLEP and ThuLEP) are size independent, while other techniques (like PVP, aquablation, WAVE, TUMT, TUVP, PUL) are especially targeted at small to medium sized prostates and TUIP only to small prostates. In regard to prostate volume, please correct the following to reflect the AUA BPH guidelines: PUL may be offered as an option for patients with LUTS attributed to BPH provided prostate volume <80g		The effort to synthesize information in a discussion of such a ponderous report often did not allow to be extremely specific on each of the 21 technologies. We think that the statement as it reads now can be accepted as prostate size < 80 g is generally considered from small (if it is < 30-40 g) to medium.

	292		Over 20% of patients were lost to follow-up in the PUL arm and only 10% in the TURP arm. The statement above is false, please refer to the published consort diagram and correct to: Of the 45 subjects that underwent PUL, 4 were censored due to surgical retreatment (PUL retreatment n=2; laser n=1) or protocol deviation (n=1). Of the subjects treated with TURP, 2 were censored due to surgical retreatment (laser n=1; botox n=1) and 1 subject withdrew. No PUL subjects were lost to follow up and the attrition bias should be low.	1	There was actually a mistake: over 20% difference between randomised and assessed patients should refer to TURP, whereas for PUL assessed patients are <5% (44/46 according to the flowchart available in Sonksen 2015). Our judgement on attrition bias is of high risk considering the difference in attrition between the two groups: we are not just looking at attrition in the PUL arm but at the assessment of outcomes in a comparative trial, therefore the differential attrition is a relevant issue